



UNIVERSITÀ
DEGLI STUDI
DI TORINO



POLITECNICO
DI TORINO

XXXI° PhD Course
Bioengineering and Medical-Surgical Sciences

**Development of a novel technology platform for
thoracoscopic aortic valve replacement**

Alberto Clerici, MD

PhD Tutor: Prof. Mauro Rinaldi

PhD Coordinator: Prof. Gianluca Ciardelli

Author Informations:

Dr. Alberto Clerici

albertclerici@gmail.com

Departement of Cardiovascular and Thoracic Surgery (Prof. Mauro Rinaldi)

University of Torino

C.so Bramante 88, Torino – Italia

Published papers 2015-2018:

- Villa, E., **Clerici, A.**, Messina, A., Testa, L., Bedogni, F., Moneta, A., ... & Troise, G. (2016). Risk factors for permanent pacemaker after implantation of surgical or percutaneous self-expanding aortic prostheses. *J Heart Valve Dis*, 25(6), 663-671.
- Centofanti, P., Attisani, M., La Torre, M., Ricci, D., Boffini, M., **Clerici, A.**, ... & Rinaldi, M. (2017). Left Ventricular Unloading during Peripheral Extracorporeal Membrane Oxygenator Support: A Bridge To Life In Profound Cardiogenic Shock. *The journal of extra-corporeal technology*, 49(3), 201.
- Salizzoni, S., Mancuso, S., Steeds, R., Lutz, M., **Clerici, A.**, Thoenes, M., ... & Messika-Zeitoun, D. (2018). TCT-363 Impact of the heart team in decision making in patients with severe aortic stenosis—data from the IMPULSE registry. *Journal of the American College of Cardiology*, 72(13 Supplement), B147.
- **Clerici, A.**, Pellegrini, A., Sansone, F., Ceresa, F., Patanè, F. (2018). A lucky escape during a hunting accident. *The Lancet*.
- Barbero, C., Ricci, D., Marchetto, G., Cura Stura, E., **Clerici, A.**, El Qarra, S.,Filippini, C., Boffini, M., Rinaldi, M. Steps forward in minimally invasive cardiac surgery: 10-year experience
The Annals of Thoracic Surgery (paper accepted for publication)

Abstract 2015-2018 :

- 2015
Presentation at the 29th EACTS annual meeting
Risk factors for permanent pacemaker after implantation of surgical or percutaneous self-expanding aortic prostheses.
Villa, E; **Clerici, A**; Messina, A; Testa, L; Bedogni, F; Moneta, A; Donatelli, F; Troise, G.

- 2018
Presentation at the 31th EACTS annual meeting:
New surgical implication: contemporary aspects of aortic stenosis. An analysis based on the IMPULSE registry. (Speaker)
Clerici A.; Richard P.S.; Norbert F.; Tanja R.; Thoenes M.; Bramlage P.; Salizzoni S.; Davis M.Z

- 2018
Presentation at 22nd Annual Congress of the European Association of Cardiovascular Imaging (EACVI), a branch of the ESC.
Facilitated data relay in a European cohort of 2,171 patients with severe aortic stenosis (Impulse Registry).
R.P. Steeds, M. Lutz, J. Thambyrajah, A. Serra, E. Schulz, J. Maly, M. Aiello, T. Rudolph, G. Lloyd, A.S. Bortone, K.E. Hauptmann, **Clerici A.**, M. Thoenes, P. Bramlage, N. Frey, D. Messika-Zeitoun

- 2018
Presentation at Euro PCR – London Valves 2018
Actual management of patients with asymptomatic severe aortic stenosis in the TAVR era (IMPULSE registry)
S. Salizzoni, R.P. Steeds, M. Lutz, J. Thambyrajah, A. Serra, E. Schulz, J. Maly, M. Aiello, T. Rudolph, G. Lloyd, A.S. Bortone, K.E. Hauptmann, **Clerici A.**, M. Thoenes, P. Bramlage, N. Frey, D. Messika-Zeitoun

Index

- Background.....Pag 06
- Impulse International Registry.....Pag 10
- New Era in Aortic Valve Surgery: Risk factors for permanent pacemaker after
implantation of surgical or percutaneous self-expanding aortic prostheses.....Pag 20
- Minimal extracorporeal Circulation (MiECC): The COMICS Registry.....Pag 31
- Pulsatile Flow in Extracorporeal Circulation: A randomized single centre study.....Pag 39
- Developing new tools for calcium debridement.....Pag 44

BACKGROUND

Aortic stenosis (AS) still remains the most frequent valve pathology requiring surgical intervention. Moreover it is progressive, potentially life-threatening, valve disorder with a prevalence that increase with age [1-2]. After the onset of symptoms, the average life expectancy of individuals with AS decrease, unless interventional treatment is provided. [3].Surgical aortic valve replacement (AVR) or transcatheter aortic valve implantation (TAVI), for patients with severe symptomatic AS who are not considered suitable for surgery, improves survival and quality of life [4]. Nowadays, due to constant aging of the population, this kind of patients presented at the time of surgery with more comorbidity and higher surgical risk [5]. This changing in quality of cardiac surgery patients led surgeons to move on, looking for new tools and techniques to obtain maximum reducing risks.

During the last three years of PhD program in Bioengineering and Medical-Surgical Sciences the core of the research was aimed to find innovative solutions in aortic valve surgery in terms of minimal invasive technique, in order to reduce the impact of traditional surgery in treatment of this kind of pathology.

The research was aimed to analyse the overall problem starting from diagnosis, passing through studying new valve prosthesis potentiality and limitations and finally looking for new technologies that can help surgeons in this type of valvular pathology.

So we conducted several studies on different issue of aortic valve stenosis.

First, as previously said, the impact of aortic stenosis in the population is changing. Nowadays, there are few information regarding the management and the pathways of patients with aortic stenosis. For this reason, we accepted to participate and collaborate to IMPULSE registry. IMPULSE registry is a multicentre, multinational (across Europe), observational study. The aim of this registry is to well define contemporary aspects of aortic stenosis and how it is managed in an era of profound changes in aortic valve

replacement. This registry give us a clear snapshot of contemporary situation. The results are very interesting and show many aspects that require research and a more in-depth analysis of the problem.

Furthermore, not only aortic stenosis management is changing in treatment (AVR vs TAVI), but also in surgical field there are new kind of prosthesis that change some point of view in surgical approach of the pathology. In the last decade, cardiac surgery was subsequently revolutionized following the introduction of nitinol-based sutureless prostheses for aortic valve replacement (AVR). This new prosthesis carried out new problems. One of these is the major development of conduction disorder after prosthesis implantation. With this retrospective study, we wanted to clarify and identify if there were some conditions that could be lead to pacemaker implantation.

Extracorporeal circulation (ECC) remains a necessary instrument for cardiac surgery. For this reason we try to analyse the problem from two different points of view, looking for minimize the impact of ECC. First, we participate to an international randomized study in using minimal ECC (MiECC) named COMICS (Conventional versus Minimally Invasive extra-corporeal circulation in patients undergoing Cardiac Surgery). This registry try to explore and define better outcomes in using particular miniaturized system of ECC. On the other hand, we designed a single centre randomized trial in using pulsatile flow instead of continuous one in some particular kind of patients and in define surgical interventions as aortic valve replacement.

Finally, the core of PhD research was to find and develop new instruments that can help surgeons approaching minimal invasive aortic valve surgery. For this reason, we try to apply ultrasonic technology for calcium debridement. Ultrasonic vibrations destroyed and remove calcium from soft tissues without damage them. In fact at particular frequencies, soft tissues vibrate concurrently without damage instead of hard tissue as bone or calcium that are removed by the ultrasonic movement. We identify a particular kind of instrument, already used in other surgeries, that can meet our needs. This is a particular probe that, in

our opinion, could be very useful in calcium removal especially in minimal invasive aortic valve surgery.

References

- 1- Eweborn, Gry Wisthus, et al. "The evolving epidemiology of valvular aortic stenosis. the Tromsø study." *Heart* 99.6 (2013): 396-400.
- 2- Maganti, Kameswari, et al. "Valvular heart disease: diagnosis and management." *Mayo Clinic Proceedings*. Vol. 85. No. 5. Elsevier, 2010.
- 3- Schwarz, Franz, et al. "The effect of aortic valve replacement on survival." *Circulation* 66.5 (1982): 1105-1110.
- 4- Van Geldorp, M. W. A., et al. "The effect of aortic valve replacement on quality of life in symptomatic patients with severe aortic stenosis." *Netherlands Heart Journal* 21.1 (2013): 28-35.
- 5- Osnabrugge, Ruben LJ, et al. "Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study." *Journal of the American College of Cardiology* 62.11 (2013): 1002-1012

IMPULSE International Registry

In 2015 we were involved in a prospective, multicentre, multinational study. This registry involved 23 centres across 9 European countries. The aim of the study starts from the idea that nowadays there is still a paucity of European data regarding the characteristic of patients presenting with severe aortic stenosis (AS) and their contemporary management. Given the rapidly changing practice in this field, the IMPULSE registry aimed to collate prospective data from consecutive patients diagnosed with severe AS on echocardiography in hospitals throughout Europe. A second end point was to evaluate the prevalence of comorbidities and how they lead the decision making process of the heart team. At least, evaluate and analyse differences in presentation and especially management of severe AS across Europe.

AS is a progressive disease that is increasing in prevalence as the global population ages [1]. The rate at which the condition progress, varies widely between patients [2], with many remaining symptom-free for several years. In the absence of symptoms, surgical intervention is only recommended in combination with left ventricular dysfunction [3]. However, once symptoms develop, the prognosis is poor, and timely treatment is essential for prolonging survival [4]. There are now several options for treating patients with symptomatic severe AS, including surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR). The latter was developed as an alternative treatment for patients with multiple comorbidities or a level of frailty that puts them at too high a risk for SAVR [5, 6].

In 2001, the Euro Heart Survey (EHS) provided a wealth of data regarding the characteristic of patients with valvular heart disease across Europe [7]. In the years since the study was performed, however, there have been significant changes in the approach to diagnosis and management of AS, with the introduction of TAVR. Therefore, there is a need for contemporary data regarding this patients population.

Results

As previously said, this is a multicentre, prospective registry across Europe. Hospitals with all treatment modalities (SAVR, TAVI) on site, were asked to document, over one year period, patients with severe AS following first echocardiography in the hospital. A total of 2.171 patients with severe AS were enrolled between March 2015 and April 2017. Of these 1.743 (80.3%) displayed symptoms attributable to AS, and with 38.3% being NYHA III-IV. The mean age of the population was 77.9 ± 10.0 years and 48.0% was female. Overall, patients had a high comorbidity burden with a mean log. Euroscore I of $15.6 \pm 13.9\%$, 27.3% had creatinine clearance of < 50 ml/min, 15.9% atrial fibrillation and 11.4% presented with chronic lung disease. 3.2% had LVEF $< 30\%$. While 52.9% of the patients were scheduled for TAVR, 24.0% to undergo SAVR. No intervention was chosen for 31.1% of patients, but medical management / watchful waiting pursued.

The patients that were symptomatic were, on average, older and more often had atrial fibrillation, previous cardiac surgery, pulmonary hypertension, chronic lung disease or severe renal impairment. More of the symptomatic patients were frail (41.2%) than of the asymptomatic (20.2%) ($p < 0.001$), and severe frailty was displayed by 5.4% and 4.1% respectively. The proportion of symptomatic patients with predicted life-expectancy of $< 25\%$ at 2 years was more than double of the asymptomatic patients (12.5% vs 5.7%; $p = 0.0001$). Symptom status was not related to differences in measures of AS severity, ventricular size or function, except for a slightly smaller mean AVA for the symptomatic patients compared to the asymptomatic.

All the 1.743 symptomatic patients had a class I indication for valve replacement; however, 383 did not undergo procedure. Of those that received valve replacement ($n = 1250$), 810 underwent TAVR and 415 underwent SAVR. For the 428 patients without symptoms, 52 had either a class I (LVEF $< 50\%$) or a class II indication ($V_{\max} > 5.5$ m/s, PAPs > 60 mmHg) for valve replacement. Of these, 30 underwent such a procedure; 22 received TAVR and 8 received SAVR. Of the 283 patients with no class I or class II

indication for valve replacement, 105 underwent either TAVR (58) or SAVR (47). (Fig 1; Fig 2)

Moreover, there is a significant difference between countries across Europe. In fact, contemporary data from major centres across Europe showed differences in the characteristic of patients with severe AS. Furthermore, treatment pathways and preferences appear to significantly differ by region suggesting a strong impact of the healthcare environment. The data illustrate region specific areas for improvement in the severe AS treatment pathways (Fig 3).

Discussion

In this large prospective multicenter registry (IMPULSE) based on 2,171 patients with severe AS we observed that:

- 1) most patients were elderly with half of the patients over 80 years,
- 2) frailty and comorbidities were common and often multiple,
- 3) symptomatic patients are still referred late in the course of the disease with severe symptoms and/or LV dysfunction,
- 4) despite availability of TAVR, more than 20% of the symptomatic patients are denied any intervention,
- 5) more than a quarter of asymptomatic were referred for intervention in the absence of a class I or IIa indication
- 6) TAVR has become the first modality of treatment.

Taken together, despite significant improvements, management of severe AS remained suboptimal in a significant proportion of contemporary patients with severe AS.

The average age of the patients enrolled in IMPULSE (77.9 years) was much higher than that of the EHS cohort (69 years) [7], and slightly higher than that of the AS patients in

the Dutch Aortic VALve RIJNmond (AVARIJN) study, which was performed from 2006 to 2009 (72.6 years) [8]. This may indicate that European patients are developing severe AS at an older age than they were 15 years ago. We cannot exclude that the setting of tertiary hospitals vs. single practice/private practices may explain some of the observed differences. Nevertheless, these findings may have major public policy implications. While different comorbidities were recorded in the EHS and IMPULSE registry, current patients present with multiple comorbidities in addition to AS. Severe renal impairment and atrial fibrillation were particularly common in the IMPULSE cohort.

As found in the EHS over 15 years ago, the IMPULSE registry demonstrates that most patients in Europe currently reach the symptomatic stage of AS before it is diagnosed / referred. Given that over a third of patients have advanced symptoms by the time they present, consideration should be given to improve screening and increase awareness to diagnose the condition before patients reach a critical stage. The data collected for the IMPULSE registry show that symptomatic patients were older than those without symptoms and it was also found in the EHS and the AVARIJN study. It is not known whether this older age reflects reluctance on the part of the patient to complain or on the part of the primary care physician to refer the patient. Higher proportions of the symptomatic patients also displayed both greater comorbidity and frailty, which increase the risk of a poor outcome from intervention. Therefore, strategies for achieving earlier diagnosis of AS need to be investigated, especially in the context of ongoing clinical trials that assess “prophylactic” TAVR in asymptomatic patients with severe AS. (EARLY TAVR; [clinicaltrials.gov NCT03042104](https://clinicaltrials.gov/ct2/show/study/NCT03042104)).

Although all symptomatic AS patients had a class I indication for valve replacement; a quarter are still denied any intervention, even though all the patients in this study were diagnosed at tertiary hospitals capable of delivering all forms of intervention for severe AS, including TAVR and SAVR. It is not known whether the rate of non-intervention would be even higher in smaller hospitals without such access. For the symptomatic

patients that did receive a replacement valve, TAVR was performed in almost double the number of patients compared to SAVR, which reflects the older age and high comorbidity burden of this population. Nevertheless it is surprising that the fraction of symptomatic patients that denied therapy remains high, even in the era of TAVR. The number of asymptomatic patients with no indication for valve replacement, but who underwent either TAVR or SAVR, is also interesting. European guidelines state that TAVR is not recommended for asymptomatic patients [3]; yet TAVR was the treatment decision more often than SAVR. Moreover, these patients were not at higher risk than those who remained under watchful waiting, according to potential indications such as higher maximal velocity or LV mass. This discrepancy likely reflects the lack of data regarding valve replacement in asymptomatic patients and highlights a need for further research.

There were limitations to the IMPULSE registry. As an observational, cross-sectional study, the outcomes after valve intervention were not recorded. Furthermore, although treatment decisions were documented, the actual treatment that each patient underwent may have differed. Finally, it is difficult to definitively assign symptomatic status in AS as some of the symptoms may have been unspecific. The strengths of the IMPULSE registry include its prospective design and that it is the largest prospective registry to date which documents clinical characteristics and management of contemporary patients.

Conclusions

Most of the patients with severe AS that were enrolled in the IMPULSE registry were symptomatic the time that they were referred, with many severely limited by their condition. These patients were older and had multiple comorbidities, suggesting that the initial presentation of AS patients has shifted towards older patients compared to previous decades. Future studies should evaluate both strategies to improve early diagnosis and strategies for early intervention. The introduction of TAVR in the years since the EHS

has transformed the way in which patients with severe AS are managed, providing hope for patients that would in the past have had no opportunity for valve replacement.

In conclusion, from IMPULSE registry we can summarize:

- 1- Treatment pathways and treatment preferences appear significantly different by region suggesting a strong impact of the healthcare environment
- 2- TAVI/AVR was NOT performed in about 1/3 of patients
- 3- TAVI has become the first choice of treatment
- 4- Symptomatic patients are still referred late in the course of the disease
- 5- The 2017 guidelines specify that asymptomatic patients who meet the criteria for AVR can be considered for surgery, not for TAVI. IMPULSE highlights that TAVI was clearly the preferred procedure
- 6- Management of severe AS is still suboptimal in a significant proportion of contemporary patients

The present study was presented:

- At the 32nd annual EACTS meeting held in Milan last October.

19/10/2018 – Rapid Response Disclosure: Dusk or Dawn for SAVR?

New surgical implication: contemporary aspects of aortic stenosis.

An analysis based on the IMPULSE registry

- At the 22nd Annual Congress of the European Association of Cardiovascular Imaging (EACVI), a branch of the ESC. Milan

06/12/2018

Facilitated data relay in a European cohort of 2,171 patients with severe aortic stenosis (Impulse Registry).

- At Euro PCR – London Valves 2018

London 11/09/2018

Actual management of patients with asymptomatic severe aortic stenosis in the TAVR era (IMPULSE registry)

The present study was already published on Journal of the American College of Cardiology, 72(13 Supplement), B147

Impact of the heart team in decision making in patients with severe aortic stenosis–data from the IMPULSE registry. .

Salizzoni, S., Mancuso, S., Steeds, R., Lutz, M., **Clerici, A.**, Thoenes, M., ... & Messika-Zeitoun, D. (2018).

Figures and Table

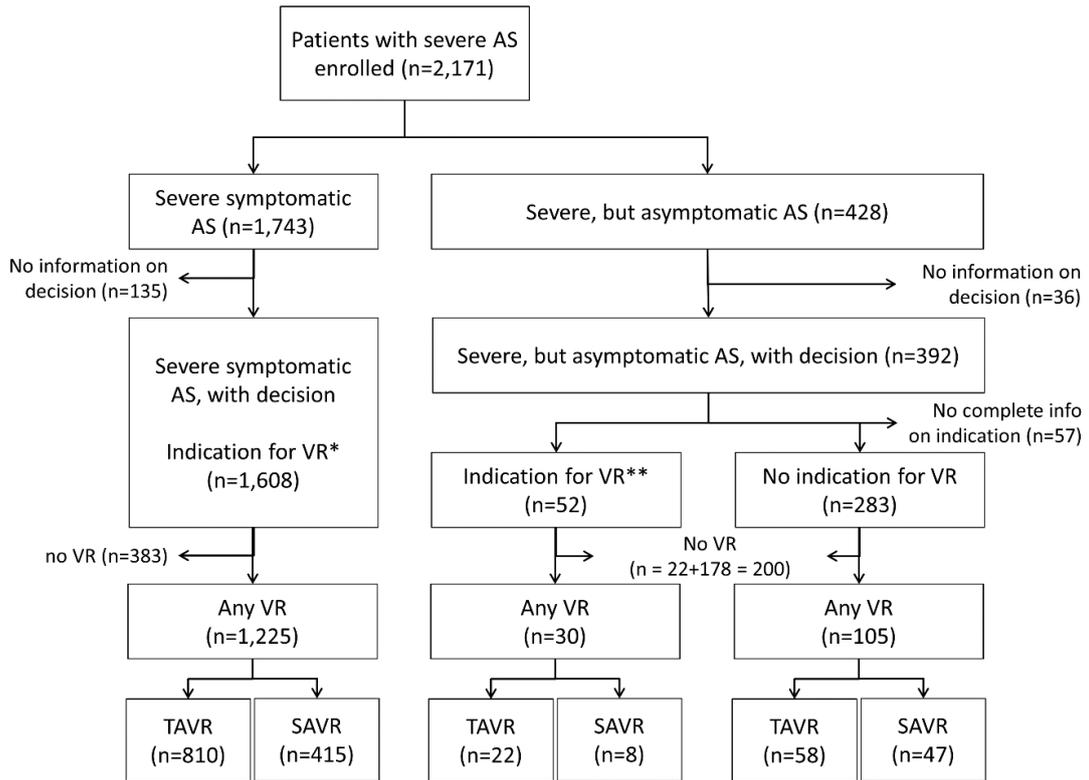


Fig. 1

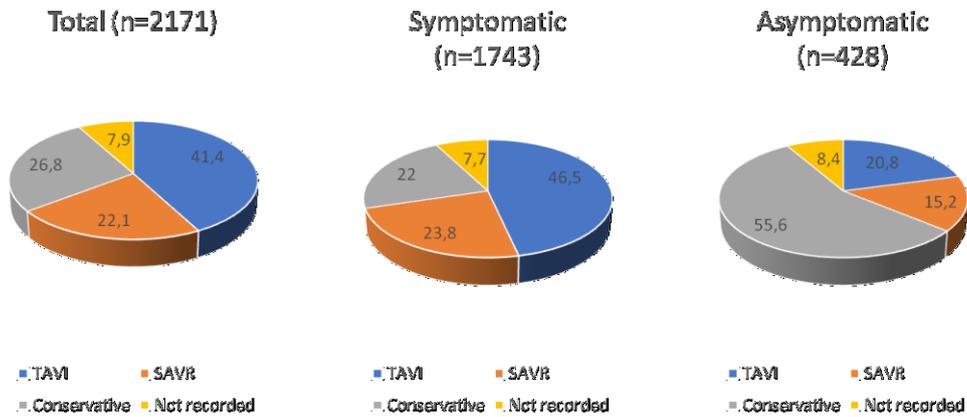


Fig 2

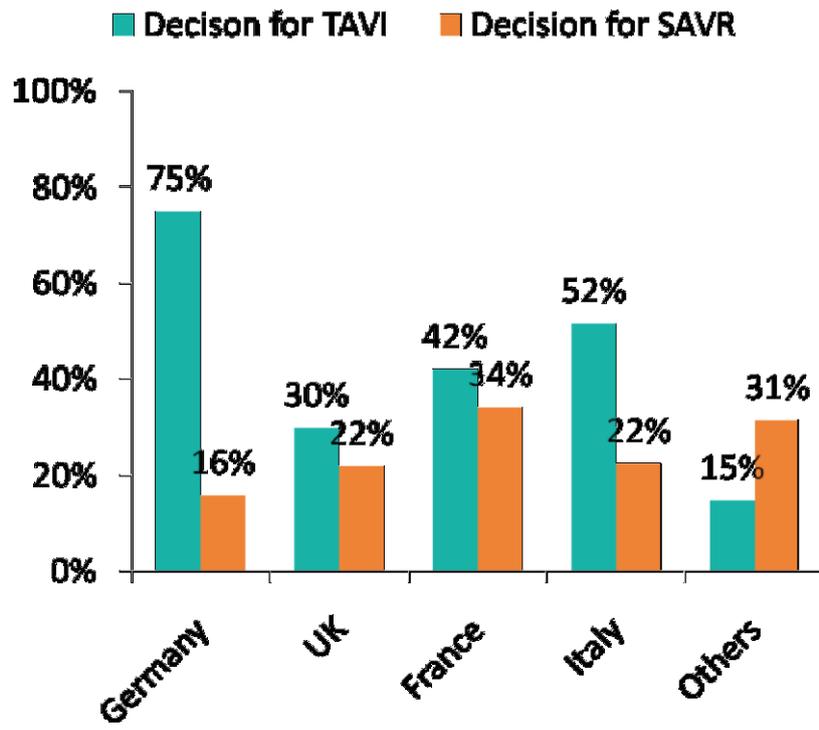


Fig 3

References

1. Maganti, Kameswari, et al. "Valvular heart disease: diagnosis and management." *Mayo Clinic Proceedings*. Vol. 85. No. 5. Elsevier, 2010.
2. Eveborn, Gry Wisthus, et al. "The evolving epidemiology of valvular aortic stenosis. the Tromsø study." *Heart* 99.6 (2013): 396-400.
3. Baumgartner, Helmut, et al. "2017 ESC/EACTS Guidelines for the management of valvular heart disease The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)." *European heart journal* 38.36 (2017): 2739-+.
4. Vahanian, Alec, et al. "Joint task force on the management of valvular heart disease of the European society of cardiology (ESC); European association for cardio-thoracic surgery (EACTS). guidelines on the management of valvular heart disease (version 2012)." *Eur Heart J* 33.19 (2012): 2451-96.
5. Cribier, Alain, et al. "Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description." *Circulation* 106.24 (2002): 3006-3008.
6. Leon, Martin B., et al. "Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery." *New England Journal of Medicine* 363.17 (2010): 1597-1607.
7. Iung, Bernard, et al. "A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease." *European heart journal* 24.13 (2003): 1231-1243.
8. Heuvelman, H. J., et al. "Clinical course of patients diagnosed with severe aortic stenosis in the Rotterdam area: insights from the AVARIJN study." *Netherlands Heart Journal* 20.12 (2012): 487-493.

New Era in Aortic Valve Surgery: Risk factors for permanent pacemaker after implantation of surgical or percutaneous self-expanding aortic prostheses

In the last two decades, aortic valve surgery has changed a lot, especially in using different kind of prosthesis. One field of research was aimed to study and to analyse a particular new type of prosthesis.

During recent years, nitinol-based technology has greatly influenced the world of biomedical devices. An extraordinary shape memory and superelastic properties are the main features of this nonferromagnetic alloy, while biocompatibility and corrosion resistance have been particularly important for the medical industry [1]. Nitinol devices also play a pivotal role in the subarea of heart valve disease therapy, where there has been a veritable revolution with the development of transcatheter aortic valve implantation (TAVI).

Improvements have been made in transcatheter procedures following the introduction of a prosthesis made with an autoexpandable nitinol stent that allows transfemoral insertion through smaller sheath sizes [2]. Cardiac surgery was subsequently revolutionized following the introduction of nitinol-based sutureless prostheses for aortic valve replacement (AVR). A completely sutureless device (which has been available since 2011) is composed of a bovine pericardial valve mounted inside an auto-expanding stent that is positioned during open-heart surgery (either standard or minimally invasive) after native valve excision [3].

One possible complication of TAVI includes complete atrioventricular block requiring permanent pacemaker (PPM) implantation, and this problem rapidly emerged as a frequent event that was related to the use of an auto-expandable prosthesis [4,5]. Even in a surgical environment, the incidence of PPM has grown with the increased use of valves

based on a nitinol stent [6]. As the identification of patients at high risk of these complications is of major clinical importance, the present study was undertaken to identify risk factors related to the need for pacemaker implantation in patients undergoing an aortic valve procedure (AVR or TAVI), using a self-expanding prosthesis.

This is a retrospective observational multicentre study. We collected 336 patients. 146 of them underwent surgical AVR using the Perceval prosthesis. On the other hand, a total of 190 patients underwent TAVI by means of the CoreValve Revalving System. Any patient with an indication for pacemaker implantation before AVR or TAVI was excluded from the study. The cardiologists/cardiac surgeons and the electrophysiologist determined the requirement for PPM implantation. Uniformly accepted indications included the continual presence of complete heart block, symptomatic bradycardia, or the need to prevent undue bradycardia while controlling tachyarrhythmias. The actual decision and timing of PPM was therefore determined based on the needs of individual patients.

The preoperative characteristics of the populations are showed in table 1.

Results

A PPM was implanted during the index hospitalization in 43 of 335 patients (12.8%) who had undergone a procedure with a nitinol-based aortic prosthesis. The patients clearly exhibited high-risk features such as advanced age, severe symptomatology and the presence of several co-morbidities, but there were no differences between the study groups except in terms of median logistic EuroSCORE (no PPM 15.59%, IQR 9.52-23.39%; PPM 20.77%, IQR 12.71- 28.06%; $p = 0.015$). A difference was observed also in terms of prevalence of statin therapy in favour of patients who did not receive a pacemaker (no PPM 34.2%, PPM 20%; $p = 0.04$). Baseline echocardiographic characteristics did not differ, while ECG profiles were unequal. Patients who required a PPM had a longer QRS interval (117 ms; IQR 95-152 ms; no PPM 98 ms, IQR 88-120 ms; $p = 0.002$) and a higher incidence of conduction disturbances (PPM 29.3% versus no

PPM 16.8%, $p = 0.034$). The distribution of these disorders differed significantly ($p = 0.007$), and a high incidence (20.9%) of right bundle branch block (RBBB) was recorded in the PPM group. The aortic valve procedure was TAVI in 56.6% of cases (190/336), and TAVI was more frequent in the group that required a definitive stimulation device (PPM 76.7% versus no PPM 53.4%, $p = 0.007$). The mean time required for a transcatheter procedure was 160 min (range: 125 to 180 min), and transfemoral access was used in 80% of patients (152/190), with the following CoreValve sizes: 23 mm = 0.6%, 26 mm = 48.9%, 29 mm = 48.9%, 31 mm = 1.7%. The rate of associated coronary intervention was 1.1% (2/190). The incidence of PPM in the TAVI subgroup was 17.5% (33/189).

AVR was the aortic valve procedure used in 43.4% of patients (146/336), and the incidence of PPM in this subgroup was 6.8% (10/146). An associated procedure was performed in 41.1% of AVR patients (60/146); of these procedures, 78.3% (47/60) were coronary artery bypass grafts. A ministernotomy approach was performed in 21.9% of patients (32/146). The prosthesis distribution, according to the label system adopted by the manufacturer, was as follows: S = 17.8%, M = 37.7%, L = 34.9%, XL = 9.6%.

The first ECG following the aortic valve procedure (Table 2) was performed when the patient arrived at the intensive care unit/coronary care unit. Eighteen patients (5.4%) were under pacemaker stimulation due to complete dependency on the device (i.e., the presence of any pacing activity in VVI mode with a lower rate of 30 beats/min). Pacemaker dependency was more frequent in the PPM group (37.6% versus 1%, $p < 0.0001$), and this group also had a longer median PR interval (208 versus 182 ms, $p = 0.007$), a longer median QRS duration (150 versus 113 ms, $p < 0.001$), a longer mean QTc interval (510.8 versus 487.3 ms, $p = 0.005$), and a higher overall incidence of conduction disorders ($p < 0.001$). Interestingly, the most frequent intra-ventricular conduction disorder in both groups, not considering the complete atrioventricular block (AVB) in the PPM group, was left bundle branch block (LBBB): 32.6% in the PPM group and 30.8% in the no PPM

group. At the end of hospitalization, more patients required a PPM compared to those who were pacemaker-dependent immediately after the procedure. Indeed, 43 patients received a pacemaker after a median time of 3.5 days (range: 1 to 6 days) following the aortic valve procedure. Of these patients, 90.7% (39/43) received a dual-chamber device and the remaining 9.3% (4/43) a single-chamber device. Surgical patients received the device later than the transcatheter group (6 days, IQR 4.8-7 days versus 3 days, IQR 0-5.3 days; $p = 0.01$). Mortality and gross morbidity was not influenced by PPM implantation. However, the median intensive care area stay was prolonged [no PPM 1 day (IQR 1-2days) versus PPM 2 days (IQR 1-3.3 days), $p = 0.016$]; the median overall stay after the aortic valve procedure was also significantly longer [no PPM 7 days (IQR 6-9 days) versus PPM 9 days (IQR 8-12 days); $p < 0.001$] (Table 3).

Discussion

The nickel-titanium alloy known as nitinol is being used increasingly in biomedical devices [1]. In the area of heart valve therapy, the TAVI procedure uses a tissue valve mounted inside a metallic stent. Although the first TAVI device was a stainless-steel balloon expandable stent, widespread use of this procedure occurred only after the commercialization of a nitinol auto-expandable device. Today, the majority of available and under-development TAVI prostheses rely on a nitinol stent [7], and TAVI has become the standard of care for inoperable patients with severe aortic stenosis, a valid alternative for those at high surgical risk, and a promising option to treat aortic regurgitation or prosthesis dysfunction. Yet, TAVI is associated with a number of adverse effects, the most common being cardiac rhythm abnormalities requiring treatment with a PPM. Of particular concern when using a nitinol-based valve has been the higher incidence of a need for PPM [4]. In cardiac surgery, where heart valve replacement has been performed by surgeons for more than 50 years, the introduction of an auto-anchoring nitinol-based prosthesis that does not require sutures has expanded the portfolio of AVR solutions [3].

The reduction of cross-clamp and CPB times, the facilitation of minimally invasive surgery and complex cardiac interventions, are expected *pari passu* with a good hemodynamic profile and lower paravalvular leak rates compared to TAVI [8]. However, along with positive outcomes, a progressive knowledge of the peri-procedural need for PPM has also been encountered in a surgical context [9]. PPM, although life-saving, has been found to reduce the benefits of aortic valve procedures, as well as adding to the specific morbidity of the device. Clearly, the cost of hospitalization and subsequent care have increased in cases of pacemaker implantation. From an historical prospective, the CoreValve and the Perceval valve (the only truly sutureless surgical prosthesis) can be considered as the prototypes of the auto-expanding devices in the fields of TAVI and AVR, respectively. For this reason, a study group was created to collect data on the implantation of nitinolbased prostheses - both surgical and percutaneous - as well as to advance the identification of high-risk patients for PPM. As each study centre offered its own series of patients, this retrospective investigation sought to identify baseline clinical, echocardiographic and electrocardiographic characteristics associated with the need for a pacemaker before discharge. ECG parameters recorded immediately after the aortic valve procedure were also considered. The overall incidence of PPM was 12.8%, which compared favorably with previous cardiological and surgical series [6,9,10]. Considering the baseline clinic characteristics, a significant difference was observed in the clinical profile summarized by the logistic EuroSCORE, with PPM patients having a general high-risk profile (EuroSCORE 20.8%). When split by treatment, comparable rates of PPM were surprisingly observed: TAVI 17.5% and AVR 6.9% in the present subgroups and TAVI 19.8% and AVR 7.1% in the subgroups of the US CoreValve High Risk Study clinical trial (models of surgical prostheses were not reported) [11]. A second element emerging from univariate statistics was that the preoperative use of statins was a protective factor for conduction disturbances. If the EuroSCORE, as an index of frailty and clinical complexity, is clearly related to morbidity, the finding on statins enriches the

debate on the pleiotropic effects of this class of drugs. On analyzing the baseline echocardiographic characteristics, no factors were found with any significant associations with PPM. Intuitively, baseline atrioventricular conduction disturbances might presuppose the need for PPM. This was confirmed in the present univariate analysis and, in particular, a wide QRS and RBBB occurred more frequently in patients that required PPM before discharge. Very few electrocardiographic investigations after the implantation of Perceval valves have been reported, although the relevance of PPM is also high in a surgical setting. It is interesting that the appearance of LBBB after the aortic valve procedure with a Nitinol device (AVR or TAVI) is relatively frequent. This phenomenon was also recorded in around one-third of patients at the first postoperative ECG. The occurrence of LBBB can be detrimental in cases of pre-existing RBBB, which would explain why RBBB has been constantly identified as a risk factor for PPM. Any clinical or ECG pre-procedural variable remained an independent predictor of PPM after logistic regression analysis in the present study. Only the fact that TAVI was the aortic valve procedure was identified as an independent risk factor for PPM. Tentative explanations can be made with the aid of biomechanics and imaging studies of the role of calcification and stent functioning. Successful deployment, anchoring and functioning of a stent-mounted valve is heavily reliant on the tissue-stent interaction, with perfectly balanced radial forces acting against the left ventricular outflow tract, and the aortic annulus and wall. This equilibrium can be profoundly altered by tissue calcification acting on the stent structure. The resulting asymmetric and non-homogeneous distribution of the radial forces challenges the present knowledge of the mechanical situation of valve stents. The advantages of AVR can therefore be related to the possibility of manual annulus decalcification. However, it was noted that the rate of PPM after AVR by means of sutureless devices was not negligible. Damage could be ascribed to the forced circularization of the aortic annulus, from its ellipsoid shape [12], performed by the auto-expanding stent thus stretching the vulnerable left bundle branches. These insights

deserve further study, possibly excluding confounding factors such as tissue edema, cardioplegia, procedural pacing and anesthetic drugs, which may influence the properties of conduction tissues. However, when ECG parameters recorded immediately after the aortic valve procedure were inserted into the statistical model, regression analysis failed to identify any independent predictors for PPM. Finally, in patients who required a pacemaker, morbidity and early mortality did not differ from that in patients who did not suffer this complication. However, the intensive care and overall post-procedural stays were significantly longer. Presumably, the overall cost of TAVI or AVR was also increased as a consequence.

Conclusion

In conclusion, nitinol technology is a groundbreaking option for use in aortic valve prostheses, both percutaneous and surgical. The radial forces of the self-expandable mechanism could be implicated in the increased need for PPM, mostly in cases of TAVI with respect to AVR. In the context of a transcatheter procedure, in-situ calcium clusters could locally load the nitinol structure, alter the distribution of forces, and provoke a localized excess of radial force that may harm the conduction tissues. In contrast, during open surgical procedures the possibility of calcium debridement and direct prosthesis sizing may preserve stent shape, and consequently assure a homogeneous energy distribution. Given the clinical and economic impact of PPM, new parameters are required to understand and preview stent/tissue interaction, and consequently to select the appropriate device. Finally, although pre-procedural conduction tissue anomalies and statin use were not independent factors for PPM, their role deserves further investigation.

The present study was presented at the 29nd annual EACTS meeting held in Amsterdam.

Risk factors for permanent pacemaker after implantation of surgical or percutaneous auto expanding aortic prosthesis.

The present study was already published on The Journal of Heart Valve Disease 2016;25:663-671

Risk Factors for Permanent Pacemaker after Implantation of Surgical or Percutaneous Self-Expanding Aortic Prostheses

Emmanuel Villa, **Alberto Clerici**, Antonio Messina, Luca Testa, Francesco Bedogni, Andrea Moneta, Francesco Donatelli, Giovanni Troise

Figure and Tables

Parameter	Total	No PPM (n = 336)	PPM (n = 292)	p-value [‡] (n = 43)
Age (years) [*]	81.8 (77.9-85.7)	81.6 (77.9-85.5)	84.1 (78.6-86.9)	0.146
Female gender (n)	203 (60.4)	176 (60.3)	26 (60.5)	0.981
Body mass index (kg/m ²) [*]	26 (23-29)	26 (23-29)	28 (23-29)	0.605
Body surface area (m ²) [*]	1.77 ± 0.2	1.77 ± 0.2	1.78 ± 0.2	0.921
Hypertension (n)	289 (86)	249 (85.3)	39 (90.7)	0.362
Diabetes (n)	109 (32.4)	90 (30.8)	19 (44.2)	0.065
	Insulin-dependent [§]	12 (11)	11 (12.2)	1 (5.3)
0.3				
Peripheral artery disease (n)	70 (20.8)	61 (20.9)	8 (18.6)	0.729
COPD (n)	51 (15.2)	41 (14)	11 (25.6)	0.084
NYHA class III/IV (n)	228 (67.9)	199 (68.2)	29 (67.4)	0.926
Dialysis (n)	13 (3.6)	12 (4.1)	1 (2.3)	0.97
Neurologic dysfunction (n)	20 (6)	16 (5.5)	4 (9.3)	0.305
Creatinine (mg/dl) [*]	1.04 (0.87-1.31)	1.02 (0.86-1.3)	1.15 (0.94-1.45)	0.066
Hemoglobin (g/dl) [*]	11.8 ± 1.52	11.86 ± 1.5	11.8 ± 1.66	0.797
Platelets (×10 ⁹ /μl) [*]	187 (154-231)	186 (154-231)	193 (159-232)	0.47
Leukocytes (×10 ⁹ /μl) [*]	6.87 (5.78-8.36)	6.88 (5.82-8.4)	6.63 (5.51-8.14)	0.537
Coronary artery disease (n)	174 (51.8)	148 (50.7)	25 (58.1)	0.361
Log EuroSCORE (%) [*]	17.04 (10.09-24.67)	15.59 (9.52-23.39)	20.77 (12.71-28.06)	0.015
Beta-blockers (n)	86 (25.6)	76 (26)	10 (21.7)	0.698
Anti-arrhythmics (n)	23 (6.8)	20 (6.9)	2 (4.7)	0.889
Statins (n)	108 (32.1)	100 (34.2)	8 (18.6)	0.04

^{*}p-values PPM versus no PPM.

^{*}Values are mean (range).

^{*}Values are mean ± SD.

[§]Percentage values refer only to diabetic patients.

Values in parentheses are percentages.

COPD: Chronic obstructive pulmonary disease.

Tab 1

Parameter	Total	No PPM (n = 335)	PPM (n = 292)	p-value (n = 43)
Pacemaker dependency (n) [‡]	18 (5.4)	3 (1)	15 (37.6)	<0.001
First rhythm				<0.001
	Sinus (n)	276 (82.4)	255 (87.2)	21 (48.8)
	Atrial fibrillation (n)	41 (12.2)	34 (11.7)	7 (16.3)
	Pacemaker (n)	18 (5.4)	3 (1)	15 (37.6)
Heart rate (bpm) [*]	72 (63-82)	72 (63-82.3)	74 (65.8-80)	0.818
PR interval (ms) [*]	184.5 (162-208)	182 (162-206)	208 (198-237.5)	0.007
First-degree AVB (n) [§]	86 (31.2)	75 (29.4)	11 (52.4)	0.029
QRS duration (ms) [*]	117 (94-146)	113 (92-142)	150 (135.5-169.8)	<0.001
QTc interval (ms) [*]	490.1 ± 47.5	487.3 ± 46	510.8 ± 53.8	0.005
Conduction disorder (n) [†]	162 (48.4)	124 (42.5)	38 (88.4)	<0.001
New conduction disorder (n) [†]	102 (37.2)	77 (31.7)	25 (83.3)	<0.001
Type of disorder [†]				<0.001
	None (n)	173 (51.6)	169 (57.9)	4 (9.3)
	AVB II or III (n)	22 (6.7)	2 (0.7)	20 (46.5)
	LBBB (n)	104 (31)	90 (30.8)	14 (32.6)
	RBBB (n)	21 (6.3)	19 (6.5)	2 (4.7)
	LAH (n)	6 (1.8)	5 (1.7)	1 (2.3)
	Bifascicular (n)	9 (2.7)	7 (2.4)	2 (4.6)
P-axis (°) [*]	53 (30.7-70)	53 (30.2-70)	48.5 (36-74)	0.891
QRS axis (°) [*]	-2 (-35.2-35)	-1 (-33-33)	-17 (-47-60)	0.755
T-axis (°) [*]	82 (40-129)	80 (40-122.7)	112 (15-148.7)	0.204

^{*}p-values PPM versus no PPM.

[‡]Pacemaker dependency refers to the presence of any pacing activity in VVI mode with a lower rate of 30 beats/min.

^{*}Values are mean (range).

Values in parentheses are percentages.

[§]Percentages relate to patients with sinus rhythm.

[†]Other than isolated first-degree AVB.

AVB: Atrioventricular block; LAH: Left anterior hemi-block; LBBB: Left bundle branch block; PM: Pacemaker; RBBB: Right bundle branch block.

Tab2

Parameter	Total (n = 335)	No PPM (n = 292)	PPM (n = 43)	p-value [‡]
Creatinine peak (mg/dl)*	1.09 (0.85-1.46)	1.08 (0.86-1.3)	1.13 (0.85-1.51)	0.782
Renal replacement therapy (n)	8 (2.4)	7 (2.4)	1 (2.4)	>0.999
Major stroke (n)	3 (0.9)	3 (1)	0 (0)	0.842
Myocardial infarction (n)	3 (0.9)	2 (0.7)	1 (2.3)	0.677
Major bleeding (n)	20 (6.0)	19 (6.6)	1 (2.3)	0.462
Intubation (h)	4 (0.8)	4.5 (0.8)	1.5 (0.7-7.6)	0.115
ICU stay (days)*	1 (1-2)	1 (1-2)	2 (1-3.3)	0.016
Post-procedural stay (days)*	7 (6-10)	7 (6-9)	9 (8-12)	<0.001
Hospital/30-day mortality (n)	15 (4.5)	13 (4.5)	2 (4.7)	>0.999

*p-values PPM versus no PPM.

†Values are mean (range).

‡Values in parentheses are percentages.

ICU: Intensive care unit.

Tab 3

References

- 1- Stoeckel, Dieter, Alan Pelton, and Tom Duerig. "Self-expanding nitinol stents: material and design considerations." *European radiology* 14.2 (2004): 292-301.
- 2- Cribier, Alain. "Development of transcatheter aortic valve implantation (TAVI): a 20-year odyssey." *Archives of cardiovascular diseases* 105.3 (2012): 146-152.
- 3- Zannis, Konstantinos, Thierry Folliguet, and François Laborde. "New sutureless aortic valve prosthesis: another tool in less invasive aortic valve replacement." *Current opinion in cardiology* 27.2 (2012): 125-129.
- 4- Erkapic, Damir, et al. "Electrocardiographic and further predictors for permanent pacemaker requirement after transcatheter aortic valve implantation." *Europace* 12.8 (2010): 1188-1190.
- 5- Khatri, Prateek J., et al. "Adverse effects associated with transcatheter aortic valve implantation: a meta-analysis of contemporary studies." *Annals of internal medicine* 158.1 (2013): 35-46.
- 6- Laborde, François, et al. "Clinical and haemodynamic outcomes in 658 patients receiving the Perceval sutureless aortic valve: early results from a prospective European multicentre study (the Cavalier Trial)." *European journal of cardio-thoracic surgery* 49.3 (2015): 978-986.
- 7- Taramasso, Maurizio, et al. "New devices for TAVI: technologies and initial clinical experiences." *Nature Reviews Cardiology* 11.3 (2014): 157.
- 8- Di Eusanio, Marco, et al. "Sutureless aortic valve replacement international registry (SU-AVR-IR): design and rationale from the International Valvular Surgery Study Group (IVSSG)." *Annals of cardiothoracic surgery* 4.2 (2015): 131.
- 9- Houthuizen, P., et al. "Postoperative conduction disorders after implantation of the self-expandable sutureless Perceval S bioprosthesis." *The Journal of heart valve disease* 23.3 (2014): 319-324.
- 10- Mazine, Amine, et al. "Sutureless aortic valve replacement: a Canadian multicentre study." *Canadian Journal of Cardiology* 31.1 (2015): 63-68.
- 11- Adams, David H., et al. "Transcatheter aortic-valve replacement with a self-expanding prosthesis." *New England Journal of Medicine* 370.19 (2014): 1790-1798.
- 12- Tops, Laurens F., et al. "Noninvasive evaluation of the aortic root with multislice computed tomography: implications for transcatheter aortic valve replacement." *JACC: Cardiovascular Imaging* 1.3 (2008): 321-330.

Minimal extracorporeal Circulation (MiECC): The COMICS Registry

Another field of research was aimed to find out alternative solutions in using a mandatory tool in cardiac surgery: extracorporeal circulation. In that field, we were involved in an international multicentre randomized controlled trial called COMICS (Conventional versus Minimally Invasive extra-corporeal circulation in patients undergoing Cardiac Surgery).

Background

Despite a fall in mortality rates over the past decades, patients having cardiac surgery continue to experience serious post-operative complications. The risk of serious and relatively common surgical complications is often a consequence of stopping the heart during the operation, using the heart and lung machine (conventional extra-corporeal circulation; CECC), and restarting and reperfusing the heart at the end of the operation. Although several strategies have been developed to reduce such complications, they still occur and can be life threatening; they also increase the length of time a patient spends in the hospital.

Morbidity occurs because surgery itself carries a risk of iatrogenic harm, primarily as a result of ischemia reperfusion injury (IRI) [1] and the systemic inflammatory response (SIR) [2]. IRI and SIR jointly increase the risk of serious and relatively common surgical complications such as acute kidney injury (AKI). IRI and SIR are unavoidable consequences (to a greater or lesser extent) of extra-corporeal circulation (cardiopulmonary bypass), cardioplegic arrest and of the subsequent reperfusion of the heart during surgery.

Although several strategies have been developed to reduce IRI and SIR (e.g. minimising the effects of perfusion and ‘conditioning’ the heart to make it more resistant to injury), [3] these harms of surgery are responsible for most post-operative complications and

consequent delays in discharge from hospital. With an ageing cardiac surgery population, more likely to have clinically significant preoperative co-morbidities (e.g. diabetes), there remains a need to develop and evaluate new interventions to reduce these iatrogenic harms.

Cardiac surgery with conventional extra-corporeal circulation (CECC) provokes a vigorous SIR due to activation of stress pathways associated with post-operative end-organ complications (e.g. heart failure, renal impairment and neurological dysfunction).[1] SIR is triggered by operative surgical trauma and IRI, but is further exacerbated by the interaction of air, blood and synthetic components in the CECC apparatus. Minimally invasive extra-corporeal circulation (MiECC) systems have been developed to reduce the inflammatory response by removing the venous reservoir, using smaller priming volumes and reducing the interface between the blood and synthetic components. Results from two RCTs suggest that MiECC reduces systemic markers of inflammation (e.g. leucocyte and cytokine release, and neutrophil activation) [4, 5].

Many RCTs, mostly small and of poor quality, have evaluated diverse MiECC systems compared to CECC [6]. The results of these RCTs have been combined in several meta-analyses, [7,8] including a recent network meta-analysis which included comparisons with off-pump coronary artery bypass, i.e. avoiding extra-corporeal circulation altogether [6]. All of these meta-analyses concluded that MiECC has substantial benefits over CECC (approximately 50% reduction in risk) with respect to death and in-hospital post-operative complications; the consistency between meta-analyses is unsurprising since there is substantial overlap in the included RCTs.

There are important limitations of these reviews. The MiECC systems evaluated in RCTs have used varied technologies.[6] Trial populations were mainly low risk, whereas one might expect the benefits of MiECC to be larger in a population of ‘all-comers’, including patients at high risk of experiencing post-operative complications. Most trials were small

(the largest recruited 500 patients and most recruited less than 200), at high risk of bias and reported a wide range of outcomes.

In summary, there have been many RCTs of MiECC versus CECC. These trials evaluated diverse technologies of varying complexity and degree of miniaturisation, which would be expected to give rise to heterogeneity in findings. Most RCTs have been small and mainly included participants at low risk of post-operative morbidity. Their findings may be biased due to selective reporting. Nevertheless, the available evidence suggests that MiECC may have substantial benefits over CECC with respect to post-operative complications. Therefore, there is an urgent need for a large, high quality RCT to address the uncertainty about the effectiveness of MiECC. If MiECC were showed to be effective and cost-effective in such a trial, the technology is available and could be rapidly implemented in practice.

Rationale of the Trial

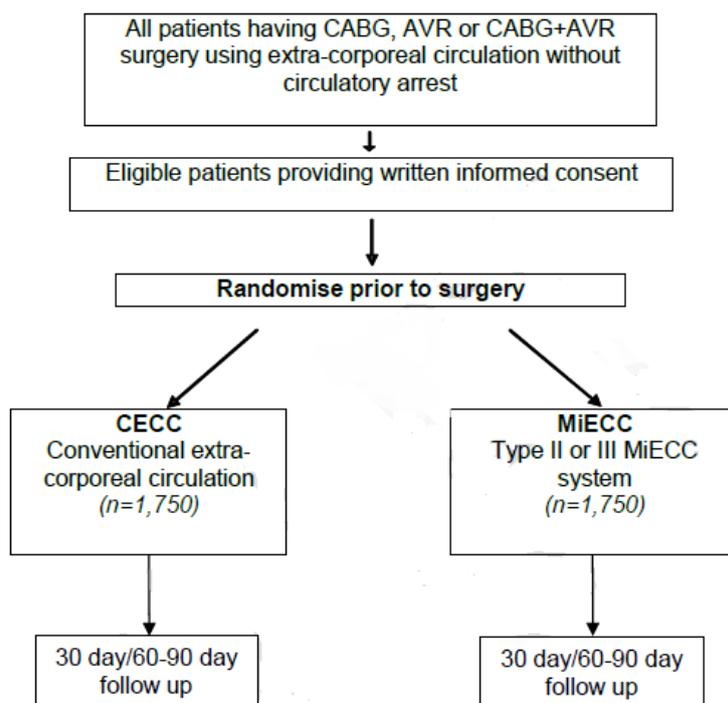
The primary hypothesis is that, compared to CECC, using MiECC during cardiac surgery reduces the proportion of patients experiencing post-operative morbidity.

The proposed trial will overcome most limitations of previous trials of MiECC. It will:

- (a) evaluate MiECC system that meet specified criteria which are used in participating centres;
- (b) be large enough to influence clinical practice, since it will be able to detect a worthwhile benefit in an outcome relevant to patients, surgeons and health services;
- (c) include a range of features to prevent bias.

The aim of the trial is to test the hypothesis that MiECC is effective and cost-effective for the majority of cardiac surgery operations requiring extra-corporeal circulation without circulatory arrest.

Trial design



This study is a multi-centre, two-group parallel randomised controlled trial to investigate the effects of using MiECC in all patients having elective or urgent coronary artery bypass grafting (CABG), aortic valve replacement (AVR) or CABG+AVR using extra-corporeal circulation without circulatory arrest. The study will be carried out in two stages: stage 1 is an internal pilot trial for 18 months (12 months recruitment) to ensure that the trial will be able to address the specified research objectives in a subset of centres.

Stage 2 is the main trial, in which additional centres will take part and during which the trial continues the recruitment until the target sample size is reached.

The research objectives will be addressed by randomising participants (1:1 ratio) to have surgery using MiECC system or CECC. Randomization will take place as close to surgery as possible and will be performed by an authorised member of the local research team not involved in post-operative data collection. Participants and members of the local research team responsible for data collection will be blind to the allocation.

One of the purpose of this trial is to use uniform sets to best avoid differences between centres in using minimal invasive extracorporeal circulation.

MiECC systems have evolved in a modular fashion, to address safety, volume and blood management issues. Systems have been classified according to their features (Types I, II, III and IV) (fig1). Centres will be allowed to use any MiECC circuit which uses CE-marked components (or components which conform to the required standards for countries outside the European Community) and which have features consistent with Type II, III or IV criteria.

Type I		Standard	<p>This closed circuit comprises of an afferent tube (blue line) which drains blood from the right atrium to the pump (⊗), then to the oxygenator (O) and returns it to the arterial circulation with the efferent tube (red line). The oblique arrow indicates cardioplegia line with its pump (⊙).</p>
Type II		Air handling	<p>A venous bubble trap/air removing device (B) is added to the standard MiECC circuit so as to facilitate air handling and avoid air entrainment to the venous line. Venting (green) lines (V) drain blood from the aortic root and/or pulmonary artery/vein.</p>
Type III		Volume management	<p>A soft shell reservoir (S) is added to the circuit to collect blood volume from the patient and return it back during perfusion according to the needs.</p>
Type IV		Blood management	<p>A hard shell reservoir (H) is added as an extra component integrated to the venous line, so as to convert the system to an open circuit that could facilitate blood management as well as overcome any other intraoperative issue (modular configuration).</p>

Fig 1

Primary and secondary outcomes

The primary outcome is a composite of post-operative complications occurring up to 30 days after randomization following the index admission.

The following events will qualify:

- death
- myocardial infarction (MI; suspected events will be documented by serum troponin concentrations and electrocardiograph recording (ECG) and adjudicated)
- stroke (report of brain imaging (CT or MRI), in association with new onset focal or generalised neurological deficit)
- gut infarction (diagnosed by laparotomy or post mortem)
- Acute kidney injury
- reintubation
- tracheostomy
- mechanical ventilation for >48 hours, including multiple episodes when separated by more than 12 hours
- reoperation
- percutaneous intervention
- sternal wound infection with dehiscence
- septicemia confirmed by microbiology

Secondary outcomes are:

- all-cause mortality 30 days after randomization
- other complications 30 days after randomization
- units of RBC transfused up to 30 days after randomization
- other blood products transfused up to 30 days after randomization
- time to discharge from cardiac ICU
- time to discharge from hospital

- delirium in ICU, assessed with the Intensive Care Delirium Screening Checklist for up to 5 days; this outcome will only be collected in a subset of participating hospitals that have the capability to do so.
- HRQoL using the EQ-5D-5L [18] up to 90 days after randomization; responses to this instrument can be mapped on to 'valuations' for the economic evaluation
- health and social care resources and associated costs up to 90 days after randomization

This international randomized trial has not started yet.

Despite this, we start to use mini-ECC system routinely, especially in aortic valve surgery and coronary artery bypass surgery.

To get information regarding this multicentre randomized trial and to learn and improve our minimal invasive extracorporeal circulation knowledge I attended at the 2nd MiEcTiS Symposium

Congress and techno-college of MIECTiS (minimal invasive extracorporeal circulation technologies international society)

Athens, June 2016, MIECTIS, Atene, from 09/06/2016 to 10/06/2016

References

- 1- Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. *New Engl J Med* 2007; 357:1121-1135.
- 2- Day JR, Taylor KM. The systemic inflammatory response syndrome and cardiopulmonary bypass. *Int J Surg.* 2005;3(2):129-40.
- 3- Beyersdorf F. The use of controlled reperfusion strategies in cardiac surgery to minimize ischaemia/reperfusion damage. *Cardiovasc Res.* 2009 Jul 15;83(2):262-8.
- 4- Ohata T, Mitsuno M, Yamamura M, Tanaka H, Kobayashi Y, Ryomoto M, et al. Minimal cardiopulmonary bypass attenuates neutrophil activation and cytokine release in coronary artery bypass grafting. *J Artif Organs.* 2007;10(2):92-5.
- 5- Beghi C, Nicolini F, Agostinelli A, Borrello B, Budillon AM, Bacciottini F, et al. Mini-cardiopulmonary bypass system: results of a prospective randomized study. *Ann Thorac Surg.* 2006 Apr;81(4):1396-400.
- 6- Kowalewski M, Pawlitzak W, Raffa GM, Malvindi PG, Kowalkowska ME, Zaborowska K et al. Safety and efficacy of miniaturized extracorporeal circulation when compared with off-pump and conventional coronary artery bypass grafting: evidence synthesis from a comprehensive Bayesian framework network meta-analysis of 134 randomized controlled trials involving 22778 patients. *Eur J Cardiothorac Surg* 2015;pii:ezv387.
- 7- Biancari F, Rimpiläinen R. Meta-analysis of randomised trials comparing the effectiveness of miniaturised versus conventional cardiopulmonary bypass in adult cardiac surgery. *Heart.* 2009 Jun;95(12):964-9.
- 8- Anastasiadis K, Antonitsis P, Haidich AB, Argiriadou H, Deliopoulos A, Papakonstantinou C. Use of minimal extracorporeal circulation improves outcome after heart surgery; a systematic review and meta-analysis of randomized controlled trials. *Int J Cardiol* 2013;164:158-69

Pulsatile Flow in Extracorporeal Circulation: A randomized single centre study

Continuous flow in extracorporeal circulation during cardiac surgery operation remain one of the most determinants in acute organ failure after interventions. A valid alternative proposed in past few years is pulsatile flow.

It is well known that ECC gives important changes in physiological blood flow into the body. Brain, lungs, kidney, liver and other abdominal organs can be affected during cardiac surgery interventions. Especially the pro-inflammatory action due to blood-air contact and blood-ECC machine contact (tubes, oxygenator, cannulae). Moreover hypothermia, hemodilution and continuous blood flow can negative affect the whole body perfusion.

In particular acute kidney injury after ECC remains one of the most important topic in cardiac surgery intervention. Incidence of acute kidney injury (AKI) that need dialysis after surgery is about 1% [1]. Is well known that ECC impact in renal function [2, 3, 4]. Pulsatile flow in ECC has been proposed as a valid alternative in organ protection during cardiac surgery interventions. Pulsatile flow is more physiological than continuous, as it is similar to natural blood flow into vessels [5]. Benefits are a less systemic inflammatory response, less inotropic support, better organ perfusion, less pulmonary oedema.

Previous studies showed conflicting results. Such studies consider only patients with normal renal function. In those patients, the risk of development acute renal injury is very low.

The aim of our study is to analyse patients with previous renal injury (Glomerular Filtration Rate < 85) prior cardiac intervention. We decided to randomized patients in two arms. One arm with traditional ECC with continuous flow and the other arm with pulsatile flow ECC.

The first end-point is to evaluate the incidence of acute renal injury after cardiac surgery intervention as a reduction of 50% of the basal glomerular filtration rate (GFR).

Secondary end points are:

- 30 days mortality
- Dialysis
- Multi-organ Injury (pulmonary, brain, liver).

Preliminary results

We started enrolment at the beginning of 2018.

Nowadays we have collected 20 patients. Respectively 12 patients for pulsatile flow arm and 8 for continuous flow arm.

We decided to measure serum creatinine and GFR in four different moments. When the patient arrived in intensive unit care (T0), after 12 hours (T1), after 24 hours (T2) and after 48 hours (T3) of cardiac surgery intervention.

The mean age is $71,7 \pm 9,89$ years (73,36 vs 68,50), mean cardiac output 4,09 (4,12 vs 4,04); FE 58,22% (58% vs 58,77). Global Euroscore II is 3,12% (3,6 vs 2,36). Eleven patients had diabetes, seven in the pulsatile flow arm and four in the continuous flow arm.

All characteristics of the population are in TAB 1.

As said we registered serum creatinine and GFR in different times after cardiac surgery intervention. See Tab 2.

Preliminary results show similar trends in serum creatinine level and GFR value in the two subgroups. As showed in figure 1 and 2 the T1 level are higher than basal showing a reducing trend hours later intervention.

As the limitations of the actual number of the patients no statistical tests are been used, but we made just a descriptive analysis.

We clearly need more patients and we hope to reach the expected number at the end of this year.

Figures and Tabs

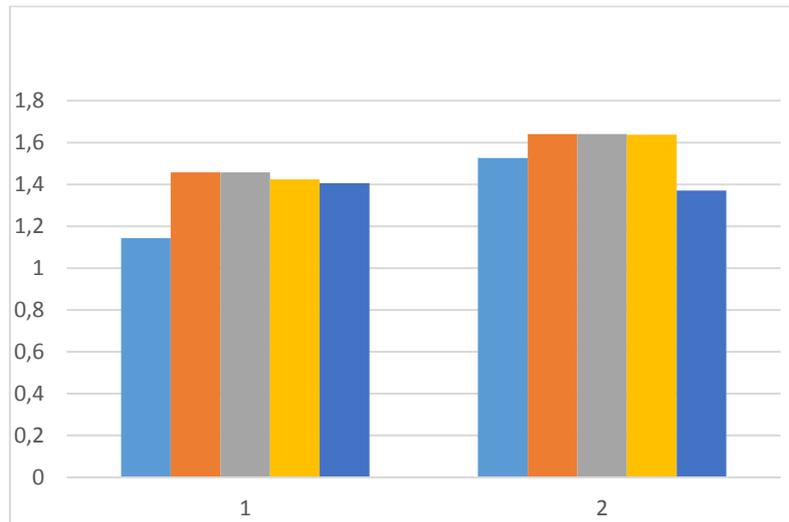
	Cumulative	Pulsatile	Continuos
Age	71.7 ± 9.8	73,36 ± 4,9	68,5 ± 16,25
Diabets	11/20 (55%)	7/12 (58.3%)	4/8 (50%)
Euroscore II (%)	3.12 ± 1.94	3,6 ± 2,25	2,36 ± 1,08
Cardiac Output (l/min)	4.09 ± 0.36	4,12 ± 0,2	4,04 ± 0,4
Ejection Fraction (%)	58.2 ± 7.2	58 ± 7,7	58,57 ± 6,9
ECC Time (min)	139.7 ± 34.7	143,36 ± 36,5	133 ± 33
Clamping Time (min)	99.3 ± 29.8	102,5 ± 31,1	93,5 ± 29,1
Preoperative Creatine	1.42 ± 0.8	1,22 ± 0,38	1,72 ± 1,18
Preoperative GRF (CG)	51.22 ± 21.53	54,1 ± 20,1	46,7 ± 24,5

Tab 1

	Cumulative	Pulsatile	Continuos
T0			
Creat	1,27	1,14	1,53
GFR	55,76	55,09	57,00
T1			
Creat	1,53	1,46	1,64
GFR	45,60	43,89	48,17
T2			
Creat	1,50	1,42	1,64
GFR	49,00	46,73	53,17
T3			
creat	1,39	1,41	1,37
GFR	53,81	51,30	58,00

T0 (access in ICU), T1 (12 hours later), T2 (24 hours later), T3 (48 hours later)

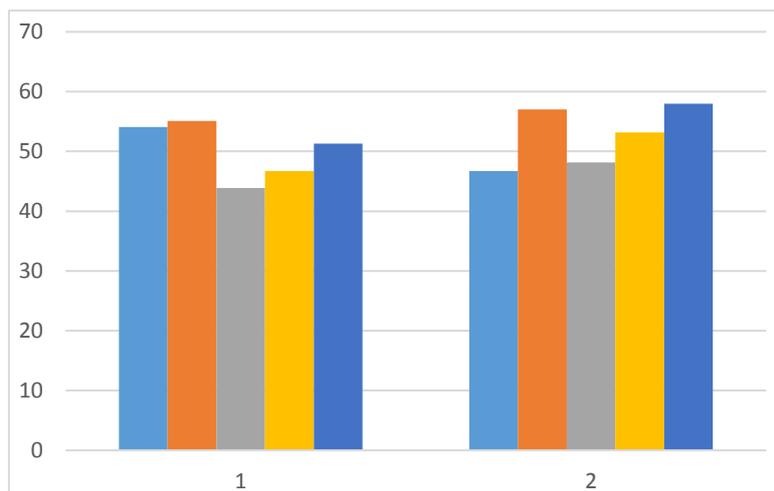
Tab 2



Pre T0 T1 T2 T3 Pre T0 T1 T2 T3
Pulsatile **Continuous**

Creatinine Serum level at different times

Fig 1



Pre T0 T1 T2 T3 Pre T0 T1 T2 T3
Pulsatile **Continuous**

GFR level at different times

Fig 2

References

- 1- Zanardo G, Michielon P, Paccagnella A, Rosi P, Caló M, Salandin V, et al. Acute renal failure in the patient undergoing cardiac operation. Prevalence, mortality rate, and main risk factors. *J Thorac Cardiovasc Surg.* 1994 Jun;107(6):1489–95
- 2- Abu-Omar Y, Ratnatunga C. *Cardiopulmonary Bypass and Renal Injury.* Perfusion. SAGE Publications; 2006 Jul 1;21(4):209–13
- 3- Karkouti K, Wijeyesundera DN, Yau TM, Callum JL, Cheng DC, Crowther M. Acute kidney injury after cardiac surgery: focus on modifiable risk factors. *Circulation.* Lippincott Williams & Wilkins; 2009 Feb 3;119(4):495–502
- 4- Doddakula K, Al-Sarraf N, Gately K, Hughes A, Tolan M, Young V, et al. Predictors of acute renal failure requiring renal replacement therapy post cardiac surgery in patients with preoperatively normal renal function. *Interact Cardiovasc Thorac Surg.* Oxford University Press; 2007 Jun 1;6(3):314–8.
- 5- Siepe M, Goebel U, Mecklenburg A, Doenst T, Benk C, Stein P, et al. Pulsatile Pulmonary Perfusion During Cardiopulmonary Bypass Reduces the Pulmonary Inflammatory Response. *The Annals of Thoracic Surgery.* Elsevier; 2008 Jul;86(1):115–22.

Developing new tools for calcium debridement

The central core of the PhD course is to think and develop new tools that can help surgeons approaching minimal invasive aortic valve surgery.

Minimally invasive techniques have recently been developed as alternative to full sternotomy to reduce the “invasiveness” of the surgical procedure, while maintaining the same quality and safety of the standard AVR approach. Less-invasive techniques include right anterior minithoracotomy (RT). Compared with conventional surgery, minimally invasive AVR has been showed to reduce postoperative mortality, morbidity, and pain while providing faster recovery, a shorter hospital stay, and better cosmetic results [1].

These changes in aortic valve surgery need development of new tools and new settings helping surgeons to ensure safe and optimal interventions.

Our idea was to think something that can help surgeons in calcium debridement through a minithoracotomy at the second intercostal space.

Nowadays traditional calcium debridement is performed mechanically with scissors and particular instruments. Calcium removal through a minimal incision is not always easy and feasible. For that reason, we try to find something that can be helpful in reaching aortic valve plane and safe in calcium debridement. After preliminary phase looking for something that could meet our needs, we try to put our attentions in ultrasonic forces.

In the early nineties there are the first experience in aortic valve decalcification using ultrasounds. The aortic valve debridement by ultrasound in degenerative-calcific aortic stenosis appeared to be an alternative treatment for severe calcified aortic stenosis [2], but was given up because of the high incidence of restenosis and aortic regurgitation [2,3, 4].

All that studies were aimed to preserve native aortic valve leaflets trying to give back natural movement, removing aortic valve stenosis [5].

Our idea was to use ultrasonic force to remove the whole calcium especially the one at the level of aortic virtual ring.

Looking at other surgical fields (especially neurosurgery, maxilla-facial and general surgery) we find out an instrument that can meet our needs.

So we decided to use SONOPET Ultrasonic Aspirator ® (Stryker, Michigan, U.S.A.).

As previously said this kind of energy is well known in neurosurgery and maxilla-facial surgery. In fact in this type of surgery is essential to remove pathological tissue leaving sane tissues undamaged. Ultrasonic technology allows this exploiting the intrinsic impedance properties of tissue. Each tissue has different level impedance. Soft tissues have different impedances respect bones or calcified tissue. The instrument works at some level of impedance avoiding in that way a damage to other tissues (fig 1).

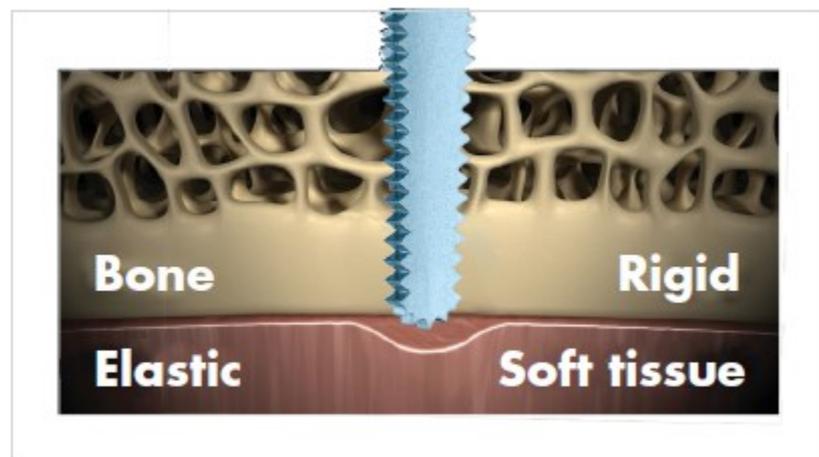


Fig 1

Aortic annulus is a very delicate part of the heart, moreover because of the structures that pass near it (fig2).

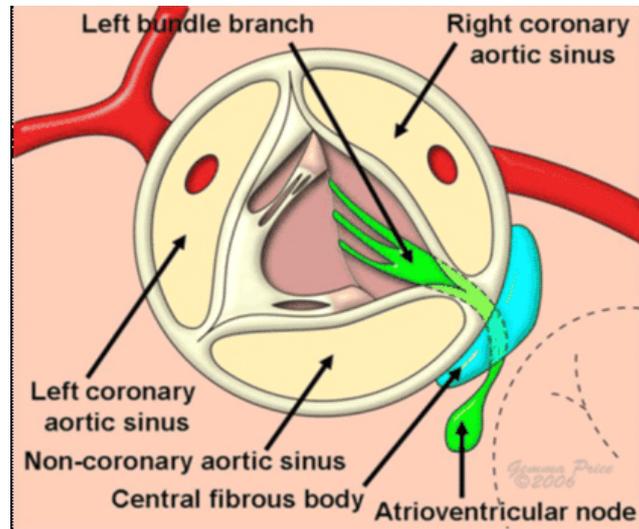


Fig 2

For that reason, the instrument must remove calcium leaving undamaged the surrounding structures.

This ultrasonic system consists of a control console with a handheld aspirator that contains a magnetostrictive transducer which converts electrical energy into mechanical motion. Moreover ultrasonic system masters fine bone and hard tissue dissection by coupling longitudinal vibration with torsional rotation (fig 3). This technology permits to emulsify bone and hard tissue (as calcified leaflets) with a high level of precision avoiding damage of the surrounding structures.

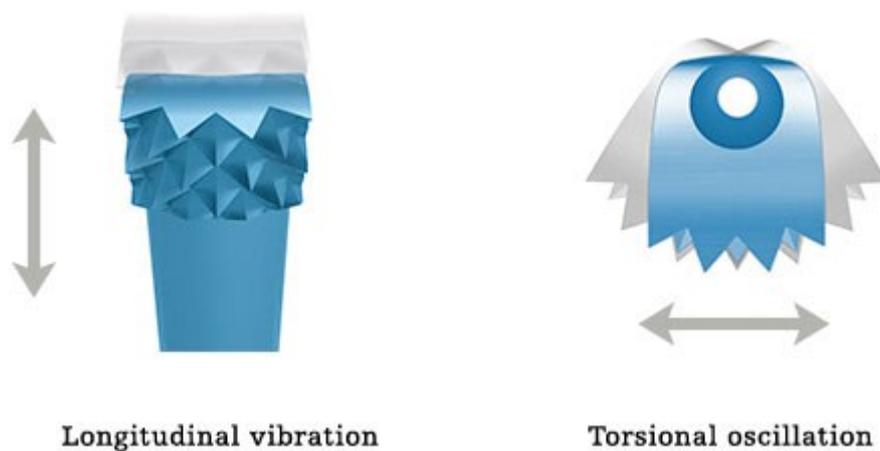


Fig 3

Furthermore, the instrument has a system of irrigation and suction.

The effects on tissue are the result of the combination of three parameters: ultrasonic energy, irrigation and suction (fig 4).

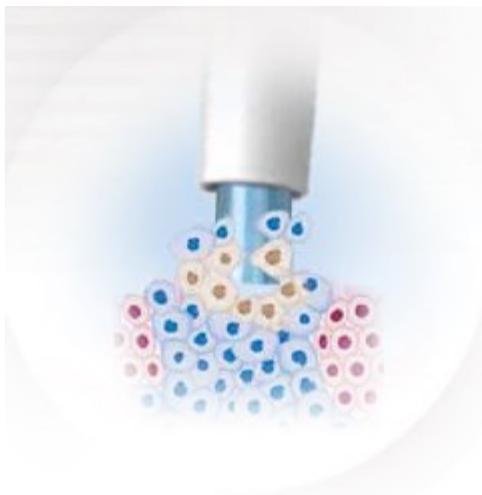


Fig 4

Our experience consist in using ultrasonic energy to decalcify aortic human valves after they had been surgically removed during an aortic valve replacement. We only conducted in vitro tests.

During this experiments we stated that ultrasonic system totally remove calcium leaving undamaged the fibrous part of aortic leaflets.

We also noted that the SONOPET ultrasonic had a very ergonomic grip. That particularly shape in our opinion is the optimum to reach aortic annulus throughout a minimal incision al the level of the second intercostal space (fig 5).



Fig 5

Moreover, the probe has numerous different tips. We find out some tips that be very useful for our purpose. A ring tip could be very useful in calcium removal at the level of aortic annulus saving other structures (fig 5).



Fig 5

Preliminary Results

Once identified the instruments, we try to test it in vitro with aortic valvular leaflets removed for traditional aortic valve replacement.

We tested the latest version of Stryke SONOPET Ultrasonic Aspirator.

Stryke SONOPET Ultrasonic Aspirator has a CE mark for neurosurgery, general surgery and maxilla-facial surgery. It has never been used in cardiac surgery.

Our idea was to get the step forward and trying it in vivo. Unfortunately we had to stop for two main reasons.

First, Stryke is trying to certify that these instruments could be used in cardiac surgery to give the permission to make tests.

Secondly, Stryke is working to a new version of SONOPET. Talking with product specialist, we decided to wait the latest version to start further tests.

We hope that the new version will be able as soon as possible to continue tests and find out new solutions in helping surgeons approaching new minimal invasive technique in aortic valvular surgery.

References

1. Schitto JD, Mokashi SA, Cohn LH. Minimally invasive valve surgery. *J Am Coll Cardiol.* 2010;56:455-62
2. Enright LP, Hancock EW, Shumway NE: Aortic debridement:longterm follow-up. *Circulation* 1971, 43:68-72
3. Craver JM: Aortic valve debridement by ultrasonic surgical aspirator: a word of caution. *Ann Thorac Surg* 1990, 49:746-52
4. Cosgrove DM, Ratliff NB, Schaff HV, Edwards WD: Aortic valve decalcification: history repeated with a new result. *Ann Thorac Surg* 1990, 49:689-90.
5. Aubert, Stéphane, et al. "A new ultrasonic process for a renewal of aortic valve decalcification." *Cardiovascular ultrasound* 4.1 (2006): 2.